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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1631	

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09/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,355	GANTIER ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-28,30-50,53-67 and 79-91* is/are pending in the application.

4a) Of the above claim(s) *12-14,19-27,39-50,56-67 and 82-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11,15-18,28,30-38,53-55,79,81,90 and 91* is/are rejected.

7)☒ Claim(s) *90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 10 June 2008 are acknowledged and the amendments are entered.

Claims 12-14, 19-27, 39-50, 56-67, and 82-89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group or Species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 16 February 2006.

Claims 1-7, 9-28, 30-50, 53-67, and 79-91 are pending and claims 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79, 81, and 90-91 are examined in this Office action.

Information Disclosure Statement

The information disclosure statement filed 10 June 2008 has been considered.

Withdrawn Rejections

The provisional rejections of claims 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79 and 81 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6-16, and 19 of copending Application No. 11/707,014 are withdrawn in view of arguments by applicants on pages 30-31 of the Remarks of 10 June 2008.

The rejections of claims 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79 and 81 under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter are

withdrawn in view of arguments by applicants on pages 30-31 of the Remarks of 10 June 2008.

Claim Objections

The following objection is newly applied and necessitated by applicant's amendments:

Claim 90 is objected to because of the following informalities:

Line 1 of instant claim 90 recites the term "highthroughput" as a single word.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following rejection is reiterated from the previous Office action:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 16 and claim 28, line 14 each recite "a restricted subset," where it is unclear as to whether this restricted subset is the same restricted subset as that recited in line 15 of claim 1 and lines 12-13 of claim 28, or a different restricted subset.

Response to Arguments:

Applicant's arguments filed 10 June 2008 have been fully considered but they are not persuasive.

Applicant argues that the second phrase regarding "a restricted subset" describes what is meant by a restricted subset in general. Applicant then argues case law stating that the failure to provide explicit antecedent basis does not always render a claim indefinite. (Ex parte Porter). However according to section 2173.05(e) of the MPEP, the result of Ex parte Porter only applies wherein the claim is reasonably ascertainable by those skilled in the art. In this instance it would have been unclear to one skilled in the art that the second "restricted subset" coincides with the same mention of "a restricted subset" recited earlier in the claim(s). It is unclear to one of skill whether the second restricted subset differs from the originally claimed "restricted subset," therefore the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 28 and 30-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Winter [US Patent 6,548,640; issued 15 April 2003; filed 26 May 1995].

Claims 28 and 30-35 are drawn to a method for generating proteins with a desired property or activity produced by generating mutants of a protein, and inserting into host cells nucleic acids which encode the mutant proteins.

The invention of Winter studies altered antibodies that have a heavy or light chain variable domain in which the framework regions differ from the framework regions naturally associated with the complementarity determining regions of the variable domain and in which the framework regions are derived from the source of framework regions that differs from the framework regions naturally associated with the complementarity determining regions of the variable regions.

Claim 28 is drawn to a method for generating proteins with a desired property or activity. As described in the abstract and Table 3 in column 20 of Winter, antibodies are studied and altered to assess activity towards antigens.

The first step of the instant claim is identifying residues in a target protein *in silico* that are associated with the property, and designating the loci of such residues is-HIT loci.

Column 21, lines 13-30 of Winter teach the use of an *in silico* generated representation of the loop of Phe27 to Tyr35 in the heavy chain variable domain of the human myeloma protein KOL which is crystallographically solved. From this *in silico* generation of the loop, Ser27 is selected to be mutated to Phe and Ser30 is selected to be mutated to Thr.

The second step of the instant method is preparing variant nucleic acid molecules encoding variant proteins, wherein each variant nucleic acid encodes a

candidate LEAD mutant protein that differs by one replacement amino acid at one is-HIT locus from the target protein wherein: the amino acid residues at each of the identified is-HIT target loci in the target protein is replaced with all of the non-native amino acids, or the amino acid residues at each of the identified is-HIT target loci in the target is replaced with a restricted subset of the remaining 19 non-native amino acids; and a restricted subset is a group of selected amino acids selected to have a predetermined effect on protein activity.

The third step of the instant method is separately introducing the nucleic acid molecules encoding each candidate LEAD protein into hosts for expression thereof, and expressing the nucleic acid molecules encoding each variant protein to produce sets of candidate LEAD proteins wherein: each candidate LEAD protein in a set contains the same amino acid replacement; each candidate LEAD protein contains a single amino acid replacement, and differs from the target protein by one amino acid replacement.

The second and third steps of the instantly rejected claims are taught in Winter in column 19, line 62 to column 20, line 7, which states:

> In stage 1, the pSVgpt vectors HuVHCAMP-RaIgG2B, and also two mutants for reasons to be explained below, HuVHCAMP(Ser27 to Phe)-RaIgG2B, HuVHCAMP(Ser27 to Phe, Ser30 to Thr)-RaIgG2B) [sic] were introduced into the heavy chain loss variant of YTH34.5HL. In stage 2, the pSVgpt vectors RaVHCAMP-RaIgG2B, RaCVHCAMP-HuIgG1, RaVHCAMP-HuIgG2, RaVHCAMP-HuIgG3, RaVHCAMP-HuIgG4 were transfected as described above. In stage 3, the pSV-gpt vector Hu(Ser27-Phe, Ser30-Thr)VHCAMP-HuIgG1 was cotransfected with the pSV-neo vector HuVLCAMP-HuIgK into the rat myeloma cell line Y0 (Y B2/3.0 Ag 20).

This passage in Winter describes the cell line used to produce the nucleic acids that transcribe into the wild type and mutant proteins taught in column 21, lines 13-30 of Winter. Each vector type produces the unique type of protein (either the original or

mutant). The amino acid serine is replaced with the amino acid phenylalanine, thus phenylalanine constitutes a "restricted subset" of amino acids used to replace the original amino acid in the unmodified protein. All of the single mutant proteins contain the same Ser27 to phenylalanine replacement.

The fourth step of the instant method individually screens each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

Table 3 of Winter in column 20 lists the results of screening the respective antibody proteins for antigen binding. Specifically, Table 3 illustrates the concentrations of antibody in ug/ml at 50% binding or lysis. In the original protein, concentration of 27.3 ug/ml is required for 50% binding while in the mutant proteins (Ser27 to Phe), 1.8 ug/ml is required for 50% binding. Consequently, the mutant LEAD protein has a much higher affinity for antigen as the original protein. Column 14, lines 52-59 and column 20, line 66 to column 22, line 12 indicate a predetermined change of binding to antigen upon mutating such residues in the "hypervariable region" including Ser27 and Ser30.

Claim 30 is further limiting wherein each of the residues at identified is-HIT loci in the target protein is replaced with codons encoding a restricted subset of the remaining 19 amino acids.

As recited in Winter in column 19, line 62 to column 20, line 7, codons are replaced in nucleic acids to encode the proteins listed in Table 3 of Winter. In this instance, a serine is replaced by a phenylalanine.

Claim 31 is further limiting wherein the total number of is-HIT loci which are replaced with replacement amino acids is less than the total number of amino acid residues within the full-length of the target protein.

In Winter, a single loci, amino acid number 27, is replaced. The protein has more than a single residue, so this substitution meets the limitations of the instant claim 31.

Claim 32 is further limiting wherein each of the residues at identified is-HIT loci in the target protein is replaced with a restricted subset of the remaining 19 amino acids; and the total number of is-HIT loci that is replaced with replacement amino acids is less that the total number of amino acid residues within the full-length of the target protein.

As taught by Winter in column 19, line 62 to column 20, line 7, codons are replaced in nucleic acids to encode the proteins listed in Table 3 of Winter. In this instance, a serine is replaced by a phenylalanine. This phenylalanine constitutes the restricted subset of the 19 remained amino acids.

In Winter, a single loci, amino acid number 27, is replaced from a serine to a single type of residue, a phenylalanine. The protein has more than a single residue, so this substitution fits the teachings of the instant claim 31.

Claim 33 is further limiting with three additional steps comprising:

--generating a population of sets of nucleic acid molecules encoding sets of candidate super-LEAD proteins wherein;

--each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins; and each set encodes a single candidate super-LEAD protein;

--introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins;

From the discussion above, one of the mutant proteins fits the description of a candidate super-LEAD protein. Specifically, the double mutant (Ser27 to Phe, Ser30 to Thr) has two mutations from the original antibody protein. This double mutant is generated from cells with vectors encoding for this double mutant.

--individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

Table 3 of column 20 of Winter tabulates the antigen screening of such a double mutant. Specifically, Table 3 illustrates the concentrations of antibody in ug/ml at 50% binding or lysis. In the original protein, concentration of 27.3 ug/ml is required for 50%

binding while in the mutant proteins (Ser27 to Phe), 1.8 ug/ml is required for 50% binding. The double mutant protein (Ser27 to Phe and Ser 30 to Phe) requires a concentration of 2.0 ug/ml for 50% binding. Consequently, the mutant LEAD protein and super-LEAD proteins have a much higher affinity for antigen as the original protein.

Claim 34 is further limiting wherein one of the types of mutations is site specific mutagenesis.

As illustrated in Table 3 in column 20 of Winter, the nucleic acids are mutated at sites corresponding to residues 27 and 30.

Claim 35 is further limiting wherein there are two positions generated from a single nucleic acid molecule. In the instance of Winter, the amino acid positions are amino acids 27 and 30, which are mutated for desired activities towards antigens.

Response to Arguments:

Applicant's arguments filed 10 June 2008 have been fully considered but they are not persuasive.

Applicant has four arguments regarding the validity of the instant anticipatory prior art rejection.

First, applicant argues that the method is a “high throughput” method, and since the method of Winter only alters a single antibody, it is not technically “high-throughput.” This argument is not found to be persuasive because absent an indication of how many

proteins processed in the method suffice as “high throughout” any amount of processed proteins/antibodies suffice as high throughput.

Second, applicant argues that the prepared nucleic acid molecules encode variant proteins (i.e. plural) where each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid at one is-HIT locus from target protein. While there are three proteins of interest in Table 3:

--HuVHCAMP

--HuVHCAMP (Ser27 to Phe)

--HuVHCAMP (Ser27 to Phe, Ser30 to Thr)

applicant is correct in that only a single mutant protein is created from the wild type and then a double mutant is created from the single mutant. However, the art is also interpretable such that if HuVHCAMP (Ser27 to Phe) is the starting point of method, each of HuVHCAMP and HuVHCAMP (Ser27 to Phe, Ser30 to Thr) is a single mutant from this HuVHCAMP (Ser27 to Phe) protein. In other words, there is no claimed limitation reciting that the starting point for the method of generating peptide molecules must start with the natural or wild type version of the protein of interest.

Consequently, the applicant’s third argument that Winter does not teach that the amino acid residues at each of the identified is-HIT target loci in the target is replaced with a restricted subset of the 19 remaining non-native amino acids is additionally not persuasive as each position of interest is replaced with a restricted subset of amino acids (i.e. amino acid 27 is replaced with the restricted subset of serine and

phenylalanine and amino acid 30 is replaced with the restricted subset of serine and threonine).

Applicant's fourth argument is also not persuasive for the same reasons as discussed above. Winter does teach sets of candidate LEAD proteins, where each candidate LEAD protein contains a single amino acid replacement and differs from the target protein by one amino acid replacement (see discussion above).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #1:

Claims 1-7, 9-11, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter as applied to claims 28, and 30-35 above, in further view of Chiang et al. [Annual Reviews in Microbiology, 1999, volume 53, pages 129-154].

Claim 1 is drawn to the same subject matter as instant claim 28, with the additional limitation of locating each of the host cells with nucleic acids encoding for the mutant proteins into a different locus on the array.

The invention of Winter teaches a method of generating a protein having a predetermined property, but does not teach use of an array.

The study of Chiang et al. investigates the in vivo genetic analysis of bacterial virulence. Specifically, one of the techniques described in Chiang et al. is the "STM" strategy diagrammed in Figures 4 and 5 of Chiang et al. on pages 140-141. In this strategy, arrays are formed where each cell expresses nucleic acids that encode specific proteins. The use of arrays by Chiang et al. allows for more systematic analysis and comparison of the mutants for the purpose in Chiang et al. of *in vivo* analysis.

Claim 2 is further limiting wherein the array comprises a solid support with separate loci and each set of cells is at a different locus.

Claim 3 is further limiting wherein the loci comprise wells; and each well contains one set of cells.

Figure 5 of Chiang et al. illustrates such microarrays with such loci comprising individual wells.

Claim 4 is further limiting wherein the nucleic acid molecules comprise plasmids, and the cells are eukaryotic cells that are transfected with the plasmids or are bacterial cells are transformed with the plasmids.

Claim 5 is further limiting wherein the nucleic acid molecules are produced by site specific mutagenesis.

The passages cited from Winter indicate that the cells that produce the antibodies are lymphoid cells transfected with plasmids with the vectors described in column 19, lines 32-47.

The site specific mutagenesis in Winter is at the codon corresponding to residue number 27 of the protein.

Claims 6 and 7 recite the same limitations as claims 33 and 34 with the exception of being dependent from two different base claims. The limitations are disclosed in Winter, as described in the 35 U.S.C. 102(e) rejection above. The array limitations are disclosed in Chiang et al.

Claim 9 is further limiting wherein the replacement amino acids correspond to the 19 remaining amino acids.

Claim 10 is further limiting wherein the nucleic acids are produced systematically be replacing each codon that is an is-HIT with one or more codons encoding a restricted subset of the remaining amino acids.

As recited in Winter in column 19, line 62 to column 20, line 7, codons are replaced in nucleic acids to encode for the proteins listed in Table 3 of Winter. In this instance, a serine is replaced by a phenylalanine.

Claim 11 is further limiting wherein the number of LEAD amino acid positions constitute two amino acid positions.

As described above, in Winter, two amino acid positions are replaced (positions 27 and 30).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the mutagenesis study of Winter by use of the array methods of Chiang et al. where the motivation would have been that the array methods of Chiang et al. allow for a more systematic means for comparing and analyzing different mutants (see, for example, pages 140-141 of Chiang et al.)

Response to Arguments:

Applicant's arguments filed 10 June 2008 have been fully considered but they are not persuasive.

Applicant continues to argue that the Winter reference is deficient for the same reasons as discussed and answered above. Applicant argues that the reference of Chiang et al. does not cure the alleged deficiencies of Winter. For the reasons discussed above, the reference of Winter is not deficient.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is stated above and reiterated below:

> It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the mutagenesis study of Winter by use of the array methods of Chiang et al. where the motivation would have been that the array methods of Chiang et al. allow for a more systematic means for comparing and analyzing different mutants (see, for example, pages 140-141 of Chiang et al.)

In response to applicant's argument that Chiang et al. is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the art of Chiang et al. and Winter are analogous because they are in the field of protein array biotechnology. There would have been a reasonable expectation of

success in applying the array methods of Chiang et al. to the assays of Winter because the actual process of the array assay, although applied to an in vivo sample, is generally applicable to any array process, including in vitro assays.

Applicant then reiterated arguments from the declaration submitted by Manuel Vega on 4 September 2007. However, these arguments are not persuasive because there is no nexus between the arguments and the claimed invention. These arguments include applicability of the method to 1000s of LEADs, performance of the preparation and screening in parallel, and the power of the method derived from the semi-rational systematic unbiased method in which by virtue of changing amino acids one-by-one, all changes are equally represented and tested. Consequently, there is no nexus between the arguments presented in the declaration because none of these argued limitations are recited in any of the limitations of the claimed methods.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #2:

Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter as applied to claims 1-7, 9-11, 15, 28, and 30-35 above, and further in view of Alam et al. [Journal of Biotechnology, volume 65, 1998, pages 183-190].

Claim 36 is further limiting wherein each is-HIT target residue is susceptible to digestion by one or more proteases.

Claim 37 is further limiting wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

Claim 38 is further limiting wherein each is-HIT target residue is resistant to digestion by one or more proteases.

The invention of Winter teaches the method of generating a protein having a predetermined property, as set forth above.

Winter does not teach use of proteolysis as a means of digestion.

In the article of Alam et al., entitled, "Expression and purification of a mutant human growth hormone that it resistant to proteolytic cleavage by thrombin, plasmin and human plasma in vitro," Alam et al. take a section of human growth hormone which is not resistant to proteolysis, and conduct mutations to the hormone to make it resistant to proteolysis (see for instant, abstract on page 183 which states, "In this study, oligonucleotide primer-directed mutagenesis was used to produce recombinant mutant hGHs resistant to limited proteolysis by these proteases.")

Susceptibility and resistance to proteolysis are determined by whether the mutation is conducted or whether the wild type is sustained, respectively.

Alam et al. ends their article in column 2 of page 189 by stating:

> This mutant GH [growth hormone] modified at the proteolytically sensitive sites is expected to have a longer period of bioavailability with characteristic pharmacological importance, implicating a potent clinical application in the future. In that case, however, the possibility that the mutant hGH may raise the antibody during the treatment has to be investigated in detail.

It would have been obvious to someone or ordinary skill in the art at the time of the instant invention to modify the method of Winter by generating proteolysis resistance mutants, as described in Alam et al. where the motivation would have to generate proteins which are expected to have a longer period of bioavailability with characteristic pharmacological importance [see column 2, page 189 of Alam et al.]

Response to Arguments:

Applicant's arguments filed 10 June 2008 have been fully considered but they are not persuasive.

Applicant argues that Alam et al. does not overcome the deficiencies of Winter discussed above. For the reasons discussed above, Winter is not deficient and the instant prior art rejection is maintained.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #3:

Claims 16-18, 53-55, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter in view of Chiang et al. as applied to claims 1-7, 9-11, 15, 28, and 30-35 above, and further in view of Alam et al. [Journal of Biotechnology, volume 65, 1998, pages 183-190].

Claim 16 is further limiting wherein each is-HIT target residue is susceptible to digestion by one or more proteases.

Claim 17 is further limiting wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

Claim 18 is further limiting wherein each is-HIT target residue is resistant to digestion by one or more proteases.

Claim 53 is further limiting wherein a predetermined property is susceptibility to digestion by proteases.

Claim 54 is further limiting wherein the LEADs possess increased resistance to proteolysis compared to unmodified target protein.

Claim 55 is further limiting wherein the predetermined property is resistance to digestion by one or more proteases.

Claim 81 is further limiting wherein the LEADs possess increased resistant to proteolysis compared to the original protein.

Winter and Chiang et al. make obvious the ability to generate LEAD proteins in arrays, as set forth above.

Winter and Chiang et al. do not teach use of proteolysis as a means of digestion.

In the article of Alam et al., entitled, "Expression and purification of a mutant human growth hormone that it resistant to proteolytic cleavage by thrombin, plasmin and human plasma in vitro," Alam et al. take a section of human growth hormone which is not resistant to proteolysis, and conduct mutations to the hormone to make it resistant to proteolysis (see for instant, abstract on page 183 which states, "In this study, oligonucleotide primer-directed mutagenesis was used to produce recombinant mutant hGHs resistant to limited proteolysis by these proteases.")

Susceptibility and resistance to proteolysis are determined by whether the mutation is conducted or whether the wild type is sustained, respectively.

Alam et al. ends their article in column 2 of page 189 by stating:

> This mutant GH [growth hormone] modified at the proteolytically sensitive sites is expected to have a longer period of bioavailability with characteristic pharmacological importance, implicating a potent clinical application in the future. In that case, however, the possibility that the mutant hGH may raise the antibody during the treatment has to be investigated in detail.

It would have been obvious to someone or ordinary skill in the art at the time of the instant invention to modify the method of Winter and Chiang et al. by generating proteolysis resistance mutants, as described in Alam et al. where the motivation would have been to generate proteins which are expected to have a longer period of bioavailability with characteristic pharmacological importance [see column 2, page 189 of Alam et al.]

Response to Arguments:

Applicant's arguments filed 10 June 2008 have been fully considered but they are not persuasive.

Applicant argues that Alam et al. does not overcome the deficiencies of Winter and Chiang et al. discussed above. For the reasons discussed above, Winter and Chiang et al. are not deficient and the instant prior art rejection is maintained.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #4:

Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Winter in view of Chiang et al. as applied to claims 1-7, 9-11, 15, 28, and 30-35 above, and further in view of Jones et al. [CABIOS, volume 8, 1992, pages 275-282].

Claim 79 is further limiting wherein the replacement amino acids are selected using Percent Accepted Mutations (PAM) matrices.

Winter and Chiang et al. make obvious the ability to generate LEAD proteins in arrays, as set forth above.

Winter and Chiang et al. do not teach PAMs.

The study of Jones et al., entitled "The rapid generation of mutation data matrices from protein sequences," shows PAM matrices on Table I on page 279 for the purpose of mutation of protein sequences.

Jones et al. explain the purpose of using these specific techniques at the end of the third full paragraph of column 1 of page 276:

> ...it is our hope that the matrices presented here will more clearly express the general nature of the underlying amino acid similarities.

It would have been obvious to someone or ordinary skill in the art at the time of the instant invention to modify the method of Winter and Chiang et al. by further use the PAMs described in Jones et al. where the motivation would have been that applying the site directed mutagenesis study to the claimed analysis condition of PAM matrices yields a clearer and more efficient understanding of the amino acid residues comprising the protein of interest (see for example, page 276 of Jones et al.)

Response to Arguments:

Applicant's arguments filed 10 June 2008 have been fully considered but they are not persuasive.

Applicant argues that Jones et al. does not overcome the deficiencies of Winter and Chiang et al. discussed above. For the reasons discussed above, Winter and Chiang et al. are not deficient and the instant prior art rejection is maintained.

The following rejection is newly applied and necessitated by amendment:

35 U.S.C. 103 Rejection #5:

Claims 90-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter in view of Chiang et al. as applied to claims 1-7, 9-11, 15, 28, and 30-35 above, and further in view of Burgess et al. [Journal of Peptide Research, volume 57, 2001, pages 68-76].

Claims 90-91 are drawn to the same subject matter as instant claim 1 with the additional limitation of requiring the subset of amino acids to be replaced to include ALL 19 of the remaining amino acids (and not just a restricted subset).

Winter and Chiang et al. make obvious the ability to generate LEAD proteins in arrays, as set forth above.

Winter and Chiang et al. do not teach that the subset of amino acids to be included in the LEAD protein generation to include all 19 of the remaining amino acids.

The study of Burgess et al. teaches diverse small size mini-libraries applied to simple and rapid epitope mapping of a monoclonal antibody.

Specifically, Figure 1 of Burgess et al. on page 71 illustrates 20 species of peptide from the library, each of which has a differing species of amino acid substituted within a single position of its sequence, and their binding affinities to a monoclonal antibody.

It would have been obvious to someone or ordinary skill in the art at the time of the instant invention to modify the method of Winter and the array methods of Chiang et

al. by use of the peptide library generation method of Burgess et al. wherein the motivation would have been that using the "combinatorial" protein library with all 20 amino acids at a single position of the sequence has the advantage of allowing more simple and rapid epitope mapping of monoclonal antibodies. [see abstract of Burgess et al.]

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the

central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin, Ph.D.
8 September 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631